Editorial

HIV therapy guidelines

Over the past few months guidelines for the treatment of HIV infection in adults have been published by groups in the United Kingdom (British HIV Association)[1] and the United States (US Department of Health and Human Services[2] and the IAS-USA panel[3]). These have been prepared in response to rapidly emerging evidence from clinical trials of the clinical benefits of combination regimens for the treatment of HIV infection. On initial review the British group appears to have taken a more conservative therapeutic approach than its United States counterparts.

However, in defining the principles of therapy there are major similarities particularly in the use of plasma HIV RNA levels (viral load) for initiating and monitoring therapy. Furthermore, guidelines are only as good as the current data on which they are based. Since the BHIVA guidelines were completed at the end of 1996 two large clinical endpoint studies have reported improved benefit of triple combination regimens compared with double nucleoside analogue combinations.

Based on data from natural history studies and clinical endpoint treatment trials all three groups emphasise the importance of measuring plasma HIV RNA and CD4 counts for determining both the risk of disease progression and response to therapy. In addition, the reduction of plasma HIV RNA to below the levels of detection of a sensitive assay is viewed as the optimal treatment response by all groups. This stems from the observation that suppression of HIV replication limits potential for selection of HIV variants that are resistant to antiretroviral drugs. Failure to suppress HIV replication adequately is likely to lead to virological and clinical failure of the treatment regimen. Each of the guidelines discusses treatment regimens that are best able to achieve this treatment goal and in the light of current data few would argue with this principle of therapy although many acknowledge that this may not be achievable in all patients.

There are, however, differences in the recommendations for initiating treatment (table) and choice of drug regimens. No clinical trial has determined the optimal time to start treatment and similar magnitudes of clinical benefit have been demonstrated at different stages of disease. In the absence of definitive data clinicians need to draw upon other levels of evidence to determine when to start treatment. Differences lie within the intepretation of this evidence and the expectation of long term benefit from current treatment regimens with the United States groups favouring earlier intervention and a heavier emphasis on the importance of plasma HIV RNA levels. If the main goal of therapy is to limit the risk of clinical progression to symptomatic disease then it seems reasonable for treatment to be offered before substantial immunodeficiency ensues and before the level of risk becomes too high. Recommendations of when to start treatment have therefore been based on studies of the natural history of HIV infection and the value of CD4 count and viral load to predict disease progression. The most influential of these have been data from the Multicentre AIDS Cohort study which demonstrated a strong association between the level of plasma HIV RNA level in early infection and long term disease progression.[4] As the US DHHS guidelines state the potential benefits of early intervention include:

(1) control of viral replication and mutation
(2) prevention of progressive immunodeficiency with a potential maintenance of a normal immune system
(3) decreased risk of selection of resistant virus and
(4) a decreased risk of drug toxicity.

Alternatively the potential risks include:

(1) a reduction in the quality of life from adverse drug effects
(2) earlier development of drug resistance
(3) limitation in future choices of antiretroviral agents
(4) unknown long term toxicity of certain drugs
(5) unknown duration of effectiveness of current antiretroviral therapies.

Although the potential benefits are admirable it remains unclear whether the complexity and potency of the current treatment regimens will achieve these goals. It is plausible that early intervention with potent and simpler treatment regimens may result in sustained clinical benefit for many years. The US DHHS guidelines encapsulate this problem of risk and benefit in the following statement:

> "A major dilemma confronting patients and practitioners is that the antiretroviral regimens currently available that have the greatest potency in terms of viral suppression, CD4 T cell preservation are medically complex, are associated with a number of specific side effects and drug interactions and pose a substantial challenge for adherence."

For many United Kingdom physicians the current level of evidence supporting early intervention is not sufficient and is outweighed by the potential risks. The protagonist of early intervention would argue that delaying therapy allows cumulative damage to the immune system and increasing diversity of the viral population, the possible prevention of both have the potential for long term benefit of treatment.

Recommendations for when to initiate antiretroviral therapy in HIV infected adults

BHIVA	*USDHHS*	*IAS-USA panel*
• Symptomatic disease • CD4 count < 300 × 10^6/l • HIV RNA > 10 000–50 000 or in range detectable to 10 000 copies/ml with falling CD4 count	• Symptomatic disease • CD4 count < 500 × 10^6/l • HIV RNA* > 20 000 copies/ml (irrespective of CD4 count)	• Symptomatic disease • CD4 count < 500 × 10^6/l • HIV RNA* 5000–10 000 copies/ml (irrespective of CD4 count)

*RT-PCR assay.

Although there may be variance over when to start therapy there is common ground over the importance of an individual patient to make an informed decision and his or her willingness to start. Several factors will influence this including known efficacy and long term safety of treatment regimens, the perceived risk of disease progression, and their ability to comply with treatment. Starting therapy is a major decision and careful thought and consideration are needed by both patient and physician if success of treatment is to be achieved.

Guidelines highlight a possible transatlantic divide over the choice of the initial treatment regimen, relating mainly to the inclusion or not of a potent protease inhibitor. The BHIVA guidelines advocate a minimum standard of care of two nucleoside analogues which the United States guidelines strongly discourage in favour of more potent triple regimens. Since the BHIVA guidelines were prepared, preliminary data have been reported from two large clinical endpoint studies showing improved benefit of the combination of zidovudine, lamivudine, and indinavir in an advanced, treatment experienced population[5] and of zidovudine, zalcitabine, and saquinavir in a mainly treatment naive population[6] compared with a combination of two nucleoside analogues. There undoubtedly has been a move towards the use of more potent triple regimens in patients starting or changing treatment regimens, particularly in patients with more advanced disease (CD4 counts less than 200 $\times$ 10^6/l) or with extensive nucleoside analogue experience or very high viral loads.

The choice of a third agent is, however, difficult as the currently licensed protease inhibitors in the United Kingdom are not ideal with respect to compliance, drug interactions, absorption, and toxicity. There is also increasing concern over the clinical impact of cross resistance between the protease inhibitors for subsequent treatment choices and their long term safety. The non-nucleoside reverse transcriptase inhibitors (NNRTIs) are an alternative; however, data on their potency in different treatment regimens are mixed. A combination of nevirapine, zidovudine, and didanosine has been shown to reduce plasma HIV RNA levels to below the limits of detection (< 500 copies/ml) in a high proportion of patients, similar to that achieved by two nucleoside analogues and a potent protease inhibitor.[7] However, no randomised clinical endpoint trial has yet shown any overall benefit from use of an NNRTI in combination and the high likelihood of cross resistance between NNRTIs is of concern. In their favour are their relative simple dosing regimens.

The recent advances in HIV therapy are to be applauded and undoubtedly further advances will ensue. In view of the increasing complexity of treatment it is essential that all clinicians involved with the care of patients with HIV continue to remain abreast of a rapidly changing knowledge base. Guidelines are useful summary statements of current knowledge and thinking but need to be taken in the context of evolving data and debate. Guidelines are no replacement for a well informed clinician fully aware of current data and their interpretation.

IAN G WILLIAMS

Department of Sexually Transmitted Diseases,
University College London Medical School,
The Mortimer Market Centre,
off Capper Street,
London WC1E 6AU

1 British HIV Association. Guidelines for Antiretroviral treatment of HIV seropositive individuals. *Lancet* 1997;**349**:1086–92.
2 Guidelines for the use of antiretroviral agents in HIV infected adults and adolescents. Washington DC: US Department of Health and Human Services, July 1997.
3 Antiretroviral therapy for HIV infection in 1997. Updated recommendations on the International AIDS society—USA panel. *JAMA* 1997; 277:1962–9.
4 Mellors JW, Munoz A, Giorgi JR, Margolick JB, Tassoni CJ, Gupta P, *et al.* Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med* 1997;**126**:946–54.
5 Hammer SM, Squires KE, Fischl MA, Hughes MD, Grimes JM, for the ACTG 320 study team. A placebo-controlled trial of indinavir in combination with two nucleoside analogues in HIV infected persons with CD4 cell counts < 200/mm^3. 8th Congress of Clinical Microbiology and Infectious Diseases, 25–28 May, Lausanne, Switzerland, (1997 ABs 90A).
6 Clumek C. For the SV 14604 study. 37th ICAAC, 28 Sept to 2 Oct 1997, Toronto, Canada.
7 Myers M, Montaner JSG for the INCAS study group. A randomised double blind comparative trial of the effects of zidovudine, didanosine and nevirapine. Combinations in antiviral naive AIDS free HIV infected patients with CD4+ cell counts 200–600/mm^3. XI International Conference on AIDS, Vancouver, Canada, 7–12 July 1996. (Abs MoB2)94.